Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19

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Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. Definitive clinical trial data are needed to identify safe and effective treatments for COVID-19. In this table, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.**

For more information on the antiviral agents that are currently being evaluated for the treatment of COVID-19, see Tables 2a and 2b.

Remdesivir

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).**

Recommendation for Patients with Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of **remdesivir** therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Chloroquine or Hydroxychloroquine

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Other Antiviral Drugs

- The Panel **recommends against** using the following drugs to treat COVID-19, except in a clinical trial:
  - The combination of **hydroxychloroquine plus azithromycin (AIII)**, because of the potential for toxicities.
  - **Lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)**, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Antiviral Therapy

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication leads to many of the clinical manifestations of COVID-19. Antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.[1] Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease, including critical illness.[2] For this reason, understanding the role of antivirals in treating mild, moderate, severe, and critical illness is necessary to optimize treatment for people with COVID-19.

The following sections describe the underlying rationale for using different antiviral medications, provide the Panel's recommendations for their roles in treating COVID-19, and summarize the existing clinical trial data. Additional antiviral therapies will be added to this section of the guidelines as new evidence emerges.

References

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Remdesivir

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Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2]

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies.

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).**

In this section, "high-flow oxygen" refers to the receipt of supplemental oxygen through a high-flow device.

Recommendation for Patients with Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some

experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Rationale

The recommendations for remdesivir are largely based on data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]). This trial included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days (or until hospital discharge, whichever came first).

Participants who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time of 11 days vs. 15 days, respectively).[3] In the preliminary subgroup analyses of ACTT, there was no observed benefit for remdesivir in people with COVID-19 who did not require oxygen supplementation; however, the number of people in this category was relatively small. Remdesivir is being evaluated in another clinical trial for the treatment of patients with moderate COVID-19; complete data from this trial are expected soon.

The preliminary analysis also reported that the patients with the clearest evidence of clinical benefit from starting remdesivir were those who required supplemental oxygen but who did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline (n = 421). In this subgroup, those who received remdesivir had a shorter time to recovery than those who received placebo (recovery rate ratio 1.47; 95% confidence interval [CI], 1.17–1.84); in a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit (hazard ratio [HR] for death 0.22; 95% CI, 0.08–0.58).

In patients who required high-flow oxygen or noninvasive ventilation at baseline (n = 197), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).

In participants who were on mechanical ventilation or ECMO at baseline (n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).

A review of the final data set, which included 28-day mortality, showed that this data set was consistent with the published preliminary data (unpublished data, based on communication from the ACTT study team to the Panel).

For patients with COVID-19 who required high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate. However, because the trial was not powered to detect differences in outcomes within these subgroups, there is uncertainty as to whether starting remdesivir confers clinical benefit in these patients. For this reason, the Panel cannot make a recommendation either for or against starting remdesivir in these patients. Because the supply of remdesivir is limited, the Panel recommends that the drug be prioritized for use in those in whom efficacy has been demonstrated (i.e., in hospitalized patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

Data from a multinational, open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit.[4] The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts consider extending the total treatment duration of remdesivir to up to 10 days in patients who do not improve after 5 days of remdesivir.[5]

Clinical Data to Date

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

ACTT is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial in hospitalized adults with COVID-19.[3] Participants were randomized 1:1 to receive IV remdesivir or placebo for 10 days. The primary study endpoint was time to clinical recovery, which was defined as either discharge from the hospital or hospitalization for infection control purposes only. Severity of illness at baseline and at Day 15 was assessed using an eight-point ordinal scale:

1. Not hospitalized, no limitations
2. Not hospitalized, with limitations
3. Hospitalized, no active medical problems
4. Hospitalized, not on oxygen
5. Hospitalized, on oxygen
6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation
7. Hospitalized, on mechanical ventilation or ECMO
8. Death

Study Population

The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection. Patients were enrolled if they met at least one of the following conditions:

- The patient had pulmonary infiltrates, as determined by radiographic imaging;
- SpO_2 was ≤94% on room air;
- The patient required supplemental oxygen;
- The patient was on mechanical ventilation; *or*
- The patient was on ECMO.

The study excluded individuals who had alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) levels >5 times the upper limit of normal (ULN), those who had an estimated glomerular filtration rate (eGFR) of <30 mL/min, and those who were pregnant or breastfeeding.

Participant characteristics

- Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the remdesivir group; n = 521 for the placebo group).
- The mean age was 58.9 years; 64.3% of participants were male, 53.2% were white, and 79.8% were enrolled in North America.
- 52.1% of participants had two or more comorbidities; 37% were obese (the mean body mass index was 30.6 kg/m^2).
- The median time from symptom onset to randomization was 9 days (interquartile range [IQR] 6–12 days).

Follow-up

- At the time of the preliminary analysis, 391 remdesivir recipients and 340 placebo recipients had completed the study through Day 29, recovered, or died.

- Eight remdesivir recipients and nine placebo recipients terminated the study prior to Day 29.
- At the time of this preliminary analysis, 132 remdesivir recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit.

Preliminary Analyses

- Remdesivir significantly reduced time to recovery compared to placebo (the median time to recovery was 11 days vs. 15 days, respectively; recovery rate ratio 1.32; 95% CI, 1.12–1.55; $P < 0.001$).
- Clinical improvement based on the ordinal scale outlined above was significantly higher at Day 15 in patients who received remdesivir than in those who received placebo (odds ratio 1.50; 95% CI, 1.18–1.91; $P < 0.001$).
- The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 421; recovery rate ratio 1.47; 95% CI, 1.17–1.84). In a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.22; 95% CI 0.08–0.58).
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 197), there was no observed difference between the remdesivir and placebo groups in time to recovery (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).
- Among patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).
- Among patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the remdesivir and placebo groups (n = 127; recovery rate ratio 1.38; 95% CI, 0.94–2.03). Mild to moderate disease was defined as SpO_2 >94% on room air and a respiratory rate of <24 breaths/min without supplemental oxygen.
- The mortality estimate by Day 14 was lower in the remdesivir arm than in the placebo arm (7.1% vs. 11.9%, respectively), but the difference was not statistically significant (HR 0.70; 95% CI, 0.47–1.04).
- The use of remdesivir was associated with a shorter time to recovery, regardless of the duration of symptoms prior to randomization (≤10 days vs. >10 days).
- The percentages of participants who experienced serious adverse events (AEs) were similar in the remdesivir and placebo groups (21.1% vs. 27.0%, respectively).
- Transaminase elevations occurred in 4.1% of remdesivir recipients and 5.9% of placebo recipients.

Limitations

- At the time of publication, the full data set was not available for analysis.

Interpretation

In patients with severe COVID-19, remdesivir reduced the time to clinical recovery. The benefit of remdesivir was most apparent in hospitalized patients who only required supplemental oxygen. There was no observed benefit of remdesivir in those who were on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. There was no observed benefit of remdesivir in patients with mild or moderate COVID-19, but the

number of participants in these categories was relatively small.

Multinational Randomized Trial of Different Durations of Remdesivir Treatment in Hospitalized Patients

This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV remdesivir. The primary study endpoint was clinical status at Day 14, which was assessed using a seven-point ordinal scale:[4]

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for remdesivir administration)
7. Not hospitalized

Study Population

The study enrolled hospitalized patients aged ≥12 years with reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates. Patients in this study had either SpO_2 ≤94% on room air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, ALT or AST levels >5 times ULN, or an estimated creatinine clearance of <50 mL/min. Patients were also excluded if they had received an agent with putative anti-SARS-CoV-2 activity within 24 hours of starting treatment in the trial.

Participant characteristics

- Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of remdesivir treatment.
- The median age, demographic characteristics, and frequency of coexisting conditions were similar between the two groups.
- The median time from symptom onset to the first dose of remdesivir was 8 days in the 5-day group and 9 days in the 10-day group. The median duration of hospitalization before the first remdesivir dose was 2 days in both groups.
- At baseline, patients in the 10-day group had worse clinical status (based on the ordinal scale distribution outlined above) than those in the 5-day group ($P = 0.02$).
- Few patients were on mechanical ventilation: Four (2%) were assigned to the 5-day group, and nine (5%) were assigned to the 10-day group. Although mechanical ventilation was an exclusion criterion for enrollment, some patients were intubated between screening and treatment initiation; others were protocol deviations.
- 172 participants (86%) in the 5-day group completed a median of 5 days of treatment, and 86 participants (44%) in the 10-day group completed a median of 9 days of treatment.

Study Endpoint Analyses

- 65% of patients in the 5-day group and 54% of those in the 10-day group had a two-point improvement in clinical status on the ordinal scale.
- After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups ($P = 0.14$).
- The time to clinical improvement of at least two levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days, respectively).
- The median duration of hospitalization among patients who were discharged on or before Day 14 was similar in the 5-day group (7 days; IQR 6–10 days) and the 10-day group (8 days; IQR 5–10 days).
- By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 (11%) had died.
- Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%). Four percent of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs.

Limitations

- This was an open-label trial without a placebo control group, so the clinical benefit of remdesivir could not be assessed.
- There were baseline imbalances in the clinical status of participants in the 5-day and 10-day groups. At the start of the study, more patients in the 10-day group than in the 5-day group were receiving noninvasive ventilation or high-flow oxygen (30% vs. 24%, respectively), and fewer patients in the 10-day group than in the 5-day group were not receiving supplemental oxygen (11% vs. 17%, respectively).

Interpretation

In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, remdesivir treatment for 5 or 10 days had similar clinical benefit. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of remdesivir treatment for critically ill patients is still unclear.

Randomized Controlled Trial of Remdesivir Versus Placebo for Severe COVID-19 in China

This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China.[6] Patients were randomized 2:1 to receive IV remdesivir or normal saline placebo for 10 days. Concomitant use of lopinavir/ritonavir, corticosteroids, and interferons was allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.

Participant Population

This study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days. These patients had SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg and radiographically confirmed pneumonia.

Results

- 237 hospitalized patients were enrolled and randomized to treatment from February 6 to March 12, 2020; 158 patients were randomized to receive remdesivir, and 79 patients were randomized to

receive placebo. The study was stopped before the target enrollment was reached due to control of the COVID-19 outbreak in China.

- The median age of the participants was 65 years; 56% of the participants in the remdesivir arm and 65% of the participants in the placebo arm were male.
- There were more patients with hypertension, diabetes, or coronary artery disease in the remdesivir arm than in the placebo arm.
- At Day 1, 83% of the participants required supplemental oxygen by nasal cannula or mask; only one participant required mechanical ventilation or ECMO.
- The median time from symptom onset to randomization was 9 days for the remdesivir group and 10 days for the placebo group.
- 65% of the participants in the remdesivir group and 68% of the participants in the placebo group received corticosteroids.
- 28% of the participants in the remdesivir group and 29% of the participants in the placebo group received lopinavir/ritonavir.
- 29% of the participants in the remdesivir arm and 38% of the participants in the placebo arm received interferon alfa-2b.

Study Endpoints

- There was no difference in the time to clinical improvement between the remdesivir and placebo groups (a median of 21 days vs. 23 days, respectively; HR 1.23; 95% CI, 0.87–1.75).
- For patients who started the study drug within 10 days of symptom onset, a faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm (a median of 18.0 days vs. 23.0 days, respectively; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant.
- The 28-day mortality was similar for the two study arms (14% and 13% of participants in the remdesivir arm and placebo arm, respectively).
- There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the two groups.
- The number of participants who experienced AEs was similar between the two groups (66% and 64% of participants in the remdesivir and placebo groups, respectively).
- More participants in the remdesivir arm than in the placebo arm discontinued therapy due to AEs (12% vs. 5% of participants in the remdesivir and placebo groups, respectively).

Limitations

- The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes.
- The use of concomitant medications (i.e., corticosteroids, lopinavir/ritonavir, interferons) may have obscured the effects of remdesivir.

Interpretation

There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between the remdesivir-treated patients and the placebo-treated patients.

Uncontrolled Case Series from Remdesivir Compassionate Use Program

In an uncontrolled case series of 53 hospitalized people with COVID-19, most patients needed less oxygen support after receiving compassionate use remdesivir. There was no comparison group, however, so it is not possible to assess whether the improvement was the result of using remdesivir.[7]

Clinical Trials

Multiple clinical trials are currently underway or in development. Please check *ClinicalTrials.gov* for the latest information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio).

Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters.

Remdesivir may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction may modestly reduce remdesivir levels. The clinical relevance of lower remdesivir levels is unknown.[8] Based on information provided by Gilead (written communication, July 2020), the use of remdesivir with strong inducers (e.g., rifampin) **is not recommended**.

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead (written communication, July 2020). Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[9]

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an eGFR of <50 mL/min are excluded from some clinical trials (some trials have an eGFR cutoff of <30 mL/min).

Considerations in Pregnancy

- Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus.[5]
- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.
- Remdesivir is available through the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for adults and children and through compassionate use programs for pregnant women and children with COVID-19.
- Ninety-eight female participants received remdesivir as part of a randomized controlled trial for the treatment of Ebola virus infection; six of these participants had a positive pregnancy test. The obstetric and neonatal outcomes were not reported in the study.[10]

Considerations in Children

- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pediatric patients.

- Remdesivir is available through an FDA EUA for adults and children and through compassionate use programs for children with COVID-19. A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier NCT04431453).
- In the same randomized controlled trial for the treatment of Ebola virus infection discussed above, 41 pediatric patients received remdesivir. These patients included neonates and children aged <18 years.[10] The safety and clinical outcomes for children were not reported separately in the published results for the trial.[11]

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Chloroquine or Hydroxychloroquine

Last Updated: June 16, 2020

Overall Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Rationale

The safety and efficacy of chloroquine and hydroxychloroquine have been evaluated in small randomized clinical trials, case series, and observational studies (as described below). Data from large randomized controlled trials are necessary to definitively determine the efficacy of chloroquine and hydroxychloroquine in treating COVID-19.

A large, retrospective, observational study that evaluated the use of hydroxychloroquine has shown no evidence of benefit in patients with COVID-19. Clinical outcomes in that study included death and the need for mechanical ventilation.[1] Reports have documented serious dysrhythmias in patients with COVID-19 who were treated with chloroquine or hydroxychloroquine, often in combination with azithromycin and other medicines that prolong the QTc interval. **Given the risk of dysrhythmias, the Food and Drug Administration (FDA) cautions against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of a hospital or clinical trial.**[2] When chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects (AEs), especially prolonged QTc interval **(AIII)**.

High-dose chloroquine (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days). A comparative trial compared high-dose chloroquine and low-dose chloroquine in patients with COVID-19; in addition, all participants received azithromycin, and 89% of the participants received oseltamivir. The study was discontinued early when preliminary results showed higher rates of mortality and QTc prolongation in the high-dose chloroquine group.[3]

Background

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946 and is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. In general, hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

- Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.[4]
- Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of SARS-CoV to the cell receptor.[5]
- *In vitro*, both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, which may be required for release of the viral genome.[6]
- Both chloroquine and hydroxychloroquine have immunomodulatory effects.

Clinical Data for COVID-19

The available clinical data on the use of chloroquine and hydroxychloroquine to treat COVID-19 mostly come from patients with mild, and, in some cases, moderate disease. Clinical data on the use of these drugs in patients with severe and critical COVID-19 are limited. The clinical data are summarized below.

Please see the Hydroxychloroquine plus Azithromycin section for additional clinical data on hydroxychloroquine.

Chloroquine

High-Dose Versus Low-Dose Chloroquine

A randomized, double-blind, Phase 2b study compared two different chloroquine regimens for the treatment of COVID 19: high-dose chloroquine (600 mg twice daily for 10 days) versus low-dose chloroquine (450 mg twice daily for 1 day followed by 450 mg for 4 days). The study participants were hospitalized adults with suspected severe COVID-19 (respiratory rate >24 rpm, heart rate >125 bpm, oxygen saturation <90%, and/or shock).[3] All patients received ceftriaxone plus azithromycin; 89.6% of patients also received oseltamivir. Of note, both azithromycin and oseltamivir can increase the QTc interval.

The primary outcome measure for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was enough to show a reduction in mortality by 50% with high-dose chloroquine. The study was stopped by the data safety and monitoring board after 81 patients were enrolled into the study.

Results:

- 41 and 40 patients were randomized into the high-dose and low-dose arms, respectively.
- The overall fatality rate was 27.2%.
- Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%] vs. in six of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (odds ratio 2.8; 95% confidence interval [CI], 0.9–8.5).
- Overall, QTcF >500 ms occurred more frequently among patients in the high-dose arm (18.9%) than in the low-dose arm (11.1%). Among those with confirmed COVID-19, QTcF >500 ms occurred more frequently in the high-dose arm (24.1%) than in the low-dose arm (3.6%).
- Two patients in the high-dose arm experienced ventricular tachycardia before death.

Limitations:

- More older patients and more patients with a history of heart disease were randomized to the high-dose arm than to the low-dose arm.

Interpretation

Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose chloroquine (600 mg twice daily) is administered in combination with azithromycin and oseltamivir.

Chloroquine Versus Lopinavir/Ritonavir

In a small randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to receive oral chloroquine 500 mg twice daily or lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days.[7] Patients with a history of heart disease (chronic disease and a history of arrhythmia), or kidney, liver, or hematologic disease were excluded from participation. The primary study

outcome was SARS-CoV-2 polymerase chain reaction (PCR) negativity at Days 10 and 14. Secondary outcomes included improvement of lung computed tomography (CT) scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety (which was determined by evaluating study drug-related AEs).

Results:

- 10 patients received chloroquine and 12 patients received lopinavir/ritonavir. At baseline, patients had good peripheral capillary oxygen saturation (SpO_2) (97% to 98%).
- Compared to the lopinavir/ritonavir-treated patients, the chloroquine-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days, $P < 0.001$).
- Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years, $P = 0.09$). Few patients had co-morbidities.
- At Day 10, 90% of the chloroquine-treated patients and 75% of the lopinavir/ritonavir-treated patients had a negative SARS-CoV-2 PCR test result. At Day 14, the percentages for the chloroquine-treated patients and the lopinavir/ritonavir-treated patients were 100% and 91.2%, respectively.
- At Day 10, 20% of the chloroquine-treated patients and 8.3% of the lopinavir/ritonavir-treated patients had CT scan improvement. At Day 14, the percentages for the chloroquine-treated patients and the lopinavir/ritonavir-treated patients were 100% and 75%, respectively.
- At Day 14, 100% of the chloroquine-treated patients and 50% of the lopinavir/ritonavir-treated patients were discharged from the hospital.
- The risk ratios of these outcome data cross 1, and the results were not statistically significant.
- Both chloroquine and lopinavir/ritonavir were generally well-tolerated.

Limitations:

- The trial sample size was very small, and the participants were fairly young.
- The chloroquine-treated patients were younger and had fewer symptoms prior to treatment initiation, which are variables that could have affected the study protocol-defined outcomes.
- Patients who had chronic co-morbidities and who were critically ill were excluded from the study.

Interpretation

In this small randomized controlled trial, chloroquine and lopinavir/ritonavir showed similar efficacy in treating COVID-19.

Hydroxychloroquine

Observational Study of Hydroxychloroquine at a Large Medical Center in New York City

This observational study evaluated 1,376 consecutive adults with COVID-19 who were admitted to a large New York City hospital (after excluding 70 patients who died or who were transferred within 24 hours after presenting to the emergency department). The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received hydroxychloroquine at baseline or during follow-up. Patients who received hydroxychloroquine were prescribed a twice-daily dose of hydroxychloroquine 600 mg on the first day and 400 mg daily for 4 additional days; this was based on the clinical guidance of the hospital.[1]

Results:

- 811 patients (58.5%) received hydroxychloroquine and 565 (41.1%) did not.

- Patients who received hydroxychloroquine were older and more likely to have hypertension (49.1% vs. 6.7%) and to be on systemic steroids (26.6% vs. 10.1%) compared with those who did not receive hydroxychloroquine.
- Patients who received hydroxychloroquine were more likely to receive concomitant azithromycin (59.9% vs. 22.5%) and/or other antibiotics (74.5% vs. 54.0%) compared with those who did not receive hydroxychloroquine.
- Patients who received hydroxychloroquine had higher levels of inflammatory markers.
- Hydroxychloroquine-treated patients had more severe hypoxia, with a lower PaO_2/FiO_2 ratio at baseline than patients who did not receive hydroxychloroquine (median of 233 mm Hg vs. 360 mm Hg).
- Most patients (85.9%) received hydroxychloroquine within 48 hours of presentation.
- Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that hydroxychloroquine use was not associated with intubation or death (hazard ratio [HR] 1.04; 95% CI, 0.82–1.32).
- There was also no association between concomitant use of azithromycin and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).

Limitations:

- Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

The use of hydroxychloroquine for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Retrospective Observational Cohort from the United States Veterans Health Administration

This study has not been peer reviewed.

An observational, retrospective cohort study analyzed data from patients with confirmed COVID-19 who were hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020.[8] Patients were categorized as having received either hydroxychloroquine, hydroxychloroquine plus azithromycin, or no hydroxychloroquine. Doses and duration of hydroxychloroquine or azithromycin use were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic, co-morbid, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if body mass index, vital signs, and discharge disposition were noted in their medical records.

Results:

- 368 patients were eligible for analysis. The patients were categorized into three treatment groups: hydroxychloroquine (n = 97; median age of 70 years), hydroxychloroquine plus azithromycin (n = 113; median age of 68 years), or no hydroxychloroquine (n = 158; median age of 69 years). All patients were male.
- 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation.
- No difference was observed between the groups in the risk of mechanical ventilation.

- Compared to the no hydroxychloroquine group, the risk of death from any cause was higher in the hydroxychloroquine group (adjusted HR 2.61; 95% CI, 1.10–6.17; $P = 0.03$), but not in the hydroxychloroquine plus azithromycin group (adjusted HR 1.14; 95% CI, 0.56–2.32, $P = 0.72$).
- There was no between-group difference in the risk of death after ventilation.

Limitations:

- The patient population was entirely male.
- The dose and duration of administration for hydroxychloroquine and azithromycin were not included in the report. Patients were included if they received a single dose of either or both drugs.
- Propensity score adjustment was used to account for differences between the groups, but the possibility of residual confounding cannot be excluded, as patients who were more ill may have been more likely to receive hydroxychloroquine.
- No imaging data were presented; severity of chest X-ray findings could predict worse outcomes.
- The use of other antiviral or immunomodulatory agents was not reported.
- The reason for the high mortality rate among patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease at admission.

Interpretation

This study showed no beneficial effect of hydroxychloroquine plus azithromycin for the treatment of COVID-19 and a possible association between hydroxychloroquine and increased mortality; however, residual confounding may have affected the study results.

Randomized Controlled Trial of Hydroxychloroquine Versus Standard of Care for Mild/Moderate COVID-19

This multicenter, randomized, open-label trial compared hydroxychloroquine 1,200 mg once daily for 3 days followed by hydroxychloroquine 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild/moderate COVID-19 [99% of the patients] and 3 weeks for two patients with severe disease) versus standard of care (SOC).[9]

The primary outcome was negative PCR within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO_2 >94% on room air, resolution of respiratory symptoms), improvement in markers of inflammation (including C-reactive protein), and improvement of lung lesions on a chest X-ray within 28 days.

Results:

- 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset.
- No difference was found between the hydroxychloroquine arm and the SOC arm in negative PCR conversion rate within 28 days (85.4% of participants vs. 81.3% of participants, respectively) or in time to negative PCR conversion (median of 8 days vs. 7 days, respectively).
- There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.
- AEs occurred in 30% of the participants in the hydroxychloroquine arm (most commonly diarrhea) versus in 9% of the participants in the SOC arm.

Limitations:

- It is unclear how the overall rate of symptom alleviation was calculated.

- The duration of hydroxychloroquine use (2 weeks) was longer than in most other observational cohort studies or clinical trials for the treatment of COVID-19.
- The study did not reach the target sample size.

Interpretation

This study demonstrated no difference in viral clearance between hydroxychloroquine and SOC.

Observational Cohort of Hydroxychloroquine Versus No Hydroxychloroquine

This observational, retrospective cohort study analyzed data for adult patients who were hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18 to 80 years were eligible if they had PCR-confirmed SARS-CoV-2 infection and required oxygen by mask or nasal cannula. Exclusion criteria included hydroxychloroquine initiation before hospitalization, receipt of another experimental COVID-19 treatment within 48 hours, organ failure that required immediate admission to the intensive care unit (ICU) or continuous care unit, admission with acute respiratory distress syndrome (ARDS) that required noninvasive ventilation with continuous positive airway pressure or mechanical ventilation, discharge from the ICU to standard care, or if a decision was made to limit or stop active treatments that were prescribed at admission. Patients in one treatment arm received a daily dose of hydroxychloroquine 600 mg within 48 hours of admission; patients in the other arm did not receive hydroxychloroquine during the same period. The decision to use hydroxychloroquine to treat a patient was based on local medical consensus and prescriber opinion, and was reportedly independent of patient characteristics. Patients were followed from baseline until death, loss to follow-up, or the end of follow-up on April 24, 2020. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization.[10]

Results:

- Of the 181 patients who were eligible for the analysis, 84 participants received hydroxychloroquine within 48 hours, eight received hydroxychloroquine beyond 48 hours, and 89 participants did not receive hydroxychloroquine.
- Co-morbidities were less common in the hydroxychloroquine group; overall initial COVID-19 severity was well balanced across the treatment arms.
- In the hydroxychloroquine group, 18% of the patients received concomitant azithromycin and 52% of the patients received amoxicillin/clavulanic acid.
- In the inverse probability of treatment weighted analysis, there was no difference in the primary outcome (survival rate without ICU transfer at Day 21) between the hydroxychloroquine group (76% of participants) and the non-hydroxychloroquine group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival and survival without ARDS at Day 21.
- Among the 84 patients who received hydroxychloroquine within 48 hours, eight patients (10%) experienced electrocardiogram (ECG) changes that required treatment discontinuation at a median of 4 days from the start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset, first-degree atrioventricular block. None of these patients received azithromycin.

Limitations:

- This was a retrospective, nonrandomized study.

Interpretation

In this retrospective study, there was no difference in clinically important outcomes between patients who

received hydroxychloroquine within 48 hours of hospital admission and those who did not.

A Case Series of Hydroxychloroquine Versus Control

In a case series from France, 26 hospitalized adults with SARS-CoV-2 infection categorized as asymptomatic or with upper or lower respiratory tract infection who received hydroxychloroquine 200 mg three times daily for 10 days were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic).[11]

Results:

- Six patients in the hydroxychloroquine group were excluded from the analysis for the following reasons:
  - One patient died.
  - Three patients were transferred to the ICU.
  - One patient stopped taking the study drug due to nausea.
  - One patient withdrew from the study.
- Six patients also received azithromycin.
- By Day 6, nasopharyngeal (NP) PCRs were negative in 14 of 20 hydroxychloroquine-treated patients (70%) and two of 16 controls (12.5%).
- Among the hydroxychloroquine patients, eight of 14 patients (57.1%) who received only hydroxychloroquine and six of six patients (100%) who received hydroxychloroquine and azithromycin had negative NP PCRs by Day 6.
- Clinical outcomes were not reported for all patients.

Limitations:

- There are several methodologic concerns with this case series:
  - The sample size of the series is small.
  - The criteria for enrollment of cases and controls is unclear.
  - Asymptomatic individuals were enrolled.
  - Exclusion of six hydroxychloroquine patients includes one death and three ICU transfers.
  - No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown.
  - The reason for the addition of azithromycin for some patients is unclear.

Interpretation

Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of hydroxychloroquine with or without azithromycin.

Adverse Effects

Chloroquine and hydroxychloroquine have a similar toxicity profile, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine.

Cardiac Adverse Effects:

- QTc prolongation, Torsade de Pointes, ventricular arrythmia, and cardiac deaths.
- The risk of QTc prolongation is greater for chloroquine than for hydroxychloroquine.

- Concomitant medications that pose a moderate to high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, macrolides [including azithromycin], fluoroquinolone antibiotics)[12] should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
- Baseline and follow-up ECGs are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.[13]
- The risk-benefit ratio should be closely assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 beats per minute), or uncorrected hypokalemia and/or hypomagnesemia.

Other Adverse Effects:

- Hypoglycemia, rash, and nausea (divided doses may reduce nausea).
- Retinopathy. Bone marrow suppression may occur with long-term use, but this is not likely with short-term use.

There is no evidence that glucose-6-phosphate dehydrogenase (G6PD) deficiency is relevant for the use of hydroxychloroquine, and G6PD testing **is not recommended**.

With chloroquine use, there is a greater risk for hemolysis in patients with G6PD deficiency. Conduct G6PD testing before initiating chloroquine. Consider using hydroxychloroquine until G6PD test results are available. If the test results indicate that the patient is G6PD deficient, hydroxychloroquine should be continued.

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors. Use caution when coadministering these drugs with medications that are metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants, digoxin).[14]

Considerations in Pregnancy

- Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE.
- Hydroxychloroquine has not been associated with adverse pregnancy outcomes in ≥300 human pregnancies with exposure to the drug.
- A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis in pregnancy.
- No dosing changes are necessary for chloroquine or hydroxychloroquine during pregnancy.

Considerations in Children

- Chloroquine and hydroxychloroquine have been used routinely in pediatric populations for the treatment and prevention of malaria and for rheumatologic conditions.

Drug Availability

- Hydroxychloroquine is approved by the FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis and is available commercially. Hydroxychloroquine is not approved for the treatment of COVID-19.

- Chloroquine is not available commercially in the United States.

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Hydroxychloroquine Plus Azithromycin

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** using **hydroxychloroquine plus azithromycin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

Chloroquine and hydroxychloroquine have been evaluated for the treatment of COVID-19 in small, randomized clinical trials, case series, and observational studies. The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly.[1]

Clinical Data in Patients With COVID-19

Please also see Chloroquine or Hydroxychloroquine, as that section includes studies in which some of the patients received azithromycin as part of their treatment.

New York Department of Health Study on Hydroxychloroquine With or Without Azithromycin

A retrospective, multicenter, observational study in New York evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into four treatment groups: hydroxychloroquine plus azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an electrocardiogram.[2]

Results

- Patients in the three treatment groups had more severe disease at baseline than those who received neither drug.
- In adjusted analyses, patients who received one of the three treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.
- Patients who received hydroxychloroquine plus azithromycin had a greater risk of cardiac arrest than patients who received neither drug (odds ratio 2.13; 95% confidence interval, 1.12–4.05).

Limitations

- Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

Despite the limitations discussed above, these findings suggest that although hydroxychloroquine and azithromycin are not associated with an increased risk of in-hospital death, the combination of hydroxychloroquine and azithromycin may be associated with an increased risk of cardiac arrest.

Case Series of Hydroxychloroquine Plus Azithromycin

In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study), patients were treated with hydroxychloroquine sulfate 200 mg three times daily for 10 days plus

azithromycin 500 mg for 1 day followed by 250 mg once daily for 4 days. The mean time from symptom onset to treatment was about 5 days. Study outcomes included the need for oxygen therapy or intensive care unit (ICU) transfer after ≥3 days of therapy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) level as determined by polymerase chain reaction (PCR) and SARS-CoV-2 culture (in a convenience sample of patients), and length of stay in the infectious diseases ward.[3]

Clinical Results

- One patient (1.2%) died, three patients (3.8%) required ICU transfer, and 12 patients (15%) required oxygen therapy.
- Sixty-five patients (81.2%) were discharged to home or transferred to other units for continued treatment; 14 patients (17.4%) were still hospitalized when the study results were published.

Laboratory Results

- Nasopharyngeal (NP) SARS-CoV-2 PCR was negative in 83% of patients by Day 7 and 93% of patients by Day 8.
- In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples.

Limitations

- This trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment.
- This trial lacked complete or longer-term follow-up.

Interpretation

The multiple issues with the trial design and the lack of a control group limit the usefulness of this study for informing recommendations.

Small Prospective Case Series of Hydroxychloroquine Plus Azithromycin

A prospective case series from France assessed 11 consecutive hospitalized patients with COVID-19.[4]

Results

- Eight of the 11 patients had significant comorbid conditions: obesity (in two patients), solid cancer (in three patients), hematological cancer (in two patients), and HIV infection (in one patient).
- Ten of the 11 patients were receiving supplemental oxygen at treatment initiation.
- All patients were treated with hydroxychloroquine 600 mg once daily for 10 days and azithromycin 500 mg once daily for 1 day followed by 250 mg once daily for 4 days.
- Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU.
- Hydroxychloroquine was discontinued in one patient due to QTc prolongation.
- Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in eight of 10 patients.

Limitations

- This case series only included 11 patients.

Interpretation

In this small case series, most patients who received hydroxychloroquine plus azithromycin did not have rapid viral clearance.

Adverse Effects

Multiple reports demonstrate that concomitant use of hydroxychloroquine and azithromycin can prolong QTc; in an observational study, hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.[5-7] The use of this combination warrants careful monitoring.

Please see Chloroquine or Hydroxychloroquine for further details regarding these drugs, including adverse effects, drug interactions, considerations in pregnant people and children, and availability.

Clinical Trials

Clinical trials that are testing the safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin in people who have or who are at risk for COVID-19 are underway in the United States and internationally. Please check *ClinicalTrials.gov* for the latest information.

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** using **lopinavir/ritonavir (AI)** or other **HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in a clinical trial.

Rationale

The pharmacodynamics of HIV protease inhibitors raise concerns about whether it is possible to achieve drug concentrations that can inhibit the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease. In addition, lopinavir/ritonavir did not show efficacy in a small randomized controlled trial in patients with COVID-19 (see below).

Lopinavir/Ritonavir

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

- Replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.[1] The enzymes responsible for this cleavage are two proteases: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).
- Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro *in vitro*, and this protease appears to be highly conserved in SARS-CoV-2.[2,3]
- Although lopinavir/ritonavir has *in vitro* activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.[4]
- Lopinavir is excreted in the gastrointestinal tract; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[5]

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

In a case series, eight patients with COVID-19 were treated with lopinavir 400 mg/ritonavir 100 mg orally twice daily and had plasma trough levels of lopinavir drawn and assayed by liquid chromatography-tandem mass spectrometry.[6]

Study Results

- The median plasma lopinavir concentration was 13.6 μg/mL.
- After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the *in vitro* half-maximal effective concentration (EC_{50}) for SARS-CoV-2.

Limitations

- Only the trough levels of lopinavir were quantified.
- No data are available on effective lopinavir concentrations for SARS-CoV-2 *in vivo*.

Interpretation

The plasma drug concentrations that were achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2.

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care for COVID-19

In a clinical trial that randomized 199 patients to receive lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days or standard of care (SOC), patients who were randomized to the lopinavir/ritonavir arm did not have a shorter time to clinical improvement.[7]

Results

- There was a lower, but not statistically significant, mortality rate for the lopinavir/ritonavir group (19.2%) than for the SOC group (25.0%), and a shorter median intensive care unit stay for those in the lopinavir/ritonavir group than those in the SOC group (6 days vs. 11 days; difference of -5 days; 95% confidence interval, -9 to 0 days).
- The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the lopinavir/ritonavir and SOC arms.
- Nausea, vomiting, and diarrhea were all more frequent in the lopinavir/ritonavir-treated group.

Limitations

- The study was not blinded, which may have affected the assessments of clinical improvement.
- The study was underpowered to show small effects.

Interpretation

A moderate-sized, randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over SOC.

Lopinavir/Ritonavir Plus Interferon Beta-1b Plus Ribavirin for COVID-19

Also see Interferons for a description of this trial and its results.

An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included interferon beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of lopinavir 400 mg/ritonavir 100 mg every 12 hours alone.

In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, interferon beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only one participant was mechanically ventilated.[8]

Study Results

- Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group.
- See the Interferons section for additional data.

Limitations

- Participants in both arms received lopinavir/ritonavir, so it is impossible to determine whether lopinavir/ritonavir contributed to the observed treatment effects. However, the possibility that lopinavir/ritonavir may have contributed to the effectiveness of the combination therapy also cannot be ruled out.

- The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset.
- Most participants in this study had mild illness: only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States.

Interpretation

This study neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Lopinavir/Ritonavir Versus Umifenovir Versus Standard of Care

In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to receive lopinavir/ritonavir, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received SOC.[9]

Results (Comparison of Lopinavir/Ritonavir to Standard of Care)

- The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar between the two groups. Patients who received lopinavir/ritonavir achieved a negative SARS-CoV-2 nucleic acid pharyngeal swab at a mean of 9 days (standard deviation [SD] ± 5.0 days) and those who received SOC achieved it at a mean of 9.3 days (SD ± 5.2 days).
- Progression to severe illness occurred among six patients in the lopinavir/ritonavir arm (18%) and two patients who received SOC (12%).
- Two patients became critically ill; both were randomized to receive lopinavir/ritonavir.

Limitations

- The trial had a small sample size.
- The study was not blinded.
- The effectiveness of umifenovir in treating COVID-19 is unknown.

Interpretation

The small sample size of this trial limits its usefulness.

Lopinavir/Ritonavir Versus Chloroquine

A small randomized study in China compared lopinavir/ritonavir to chloroquine. Please refer to the Chloroquine or Hydroxychloroquine section for the study description.[10]

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The adverse effects for lopinavir/ritonavir include:

- Nausea, vomiting, diarrhea (common)
- QTc prolongation
- Hepatotoxicity

Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A, and many medications that are

metabolized by this enzyme may cause severe toxicity. Please refer to the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV for a list of potential drug interactions.

Considerations in Pregnancy

- There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and the drug has a good safety profile.
- There is no evidence of human teratogenicity (can rule out a 1.5-fold increase in overall birth defects).
- Lopinavir has low placental transfer to the fetus. Please refer to the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.

Dosing

- Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and **is not recommended** for use during pregnancy. Please refer to the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.
- The use of once-daily dosing for lopinavir/ritonavir **is not recommended** during pregnancy.

Considerations in Children

- Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents.
- There are no data on the efficacy of using lopinavir/ritonavir to treat COVID-19 in pediatric patients.

Darunavir/Cobicistat or Darunavir/Ritonavir

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

- Darunavir inhibits the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibits the PLpro enzyme.
- In an *in vitro* study, darunavir did not show activity against SARS-CoV-2.[11]
- Results from an unpublished randomized controlled trial of 30 patients in China showed that darunavir/cobicistat was not effective in the treatment of COVID-19.[12]

Clinical Trials

There are currently no clinical trials that are evaluating the use of darunavir/cobicistat or darunavir/ritonavir in participants with COVID-19 in the United States.

Other HIV Protease Inhibitors, Including Atazanavir

There are no data from clinical trials that support the use of other HIV protease inhibitors to treat COVID-19.

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Table 2a. Potential Antiviral Agents Under Evaluation for Treatment of COVID-19: Clinical Data to Date

Last Updated: July 30, 2020

Information presented in this table may include data from pre-prints or non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Azithromycin **Note:** Most studies of COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	• Induction of IFN-stimulated genes, attenuating viral replication[2] • Enhanced neutrophil activation[3] • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells[2]	• AZM has primarily been studied for the treatment of COVID-19 in combination with HCQ. The RECOVERY trial includes an AZM monotherapy arm, which is currently enrolling. • Please see the description of the combination therapy study results in the Hydroxychloroquine Plus Azithromycin section below and in Hydroxychloroquine Plus Azithromycin.
Chloroquine	• Malaria • Extra-intestinal amebiasis	• Increases endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes[4] • Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with binding of SARS-CoV to the cell receptor[5] • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome[6] • Immunomodulatory effects	**High-Dose vs. Low-Dose CQ:**[7] • A randomized, double-blind, Phase 2b study compared 2 different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) vs. CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected cases of severe COVID-19 (respiratory rate >24 breaths/min, heart rate >125 bpm, oxygen saturation <90%, and/or shock). All patients received ceftriaxone plus AZM; 89.6% of patients received oseltamivir. Of note, both AZM and oseltamivir can increase the QTc interval. • The primary outcome for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was sufficient to show a reduction in mortality by 50% with high-dose CQ. The study was stopped by the study's DSMB after 81 patients were enrolled. *Results:* • 41 and 40 patients were randomized into the high-dose and low-dose CQ arms, respectively. • The overall fatality rate was 27.2%. • Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%]

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Chloroquine, continued			vs. in 6 of 40 patients [15%], respectively; $P = 0.03$). This difference was no longer significant when controlled by age (OR 2.8; 95% CI, 0.9–8.5). • Overall, QTcF >500 ms occurred more frequently in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients). Among those with confirmed COVID-19, QTcF >500 ms was also more frequent in the high-dose arm (24.1% of patients) than in the low-dose arm (3.6% of patients). • 2 patients in the high-dose arm experienced ventricular tachycardia before death. *Limitations:* • More older patients and more patients with history of heart disease were randomized to the high-dose arm than to the low-dose arm. *Interpretation:* • Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose CQ (600 mg twice daily) is administered in combination with AZM and oseltamivir. **CQ vs. LPV/r:**[8] • In a small, randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to receive oral CQ 500 mg twice daily or LPV/r 400 mg/100 mg twice daily for 10 days. Patients with a history of heart disease (chronic disease and a history of arrhythmia), or kidney, liver, or hematologic diseases were excluded from participation. The primary study outcome was a negative SARS-CoV-2 PCR test result at Days 10 and 14. Secondary outcomes included improvement of lung CT scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety (which was determined by evaluating study drug-related AEs). *Results:* • Ten patients received CQ and 12 patients received LPV/r. At baseline, patients had good SpO_2 levels (97% to 98%). • Compared to the LPV/r-treated patients, the CQ-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days, $P < 0.001$).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Chloroquine, continued			• Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years; $P = 0.09$). Few patients had comorbidities. • At Day 10, 90% of the CQ-treated patients and 75% of the LPV/r-treated patients had a negative SARS-CoV-2 PCR test result. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 91.2%, respectively. • At Day 10, 20% of the CQ-treated patients and 8.3% of the LPV/r-treated patients had CT scan improvement. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 75%, respectively. • At Day 14, 100% of the CQ-treated patients and 50% of the LPV/r-treated patients were discharged from the hospital. • The risk ratios of these outcome data cross 1, and the results were not statistically significant. • Both drugs were generally well tolerated. *Limitations:* • The trial sample size was very small, and the participants were fairly young. • The CQ-treated patients were younger and had fewer symptoms prior to treatment initiation; these variables could have affected the study protocol-defined outcomes. • Patients who had chronic comorbidities and who were critically ill were excluded from the study. *Interpretation:* • In this small randomized controlled trial, CQ and LPV/r showed similar efficacy in treating COVID-19.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• Increases the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes[4] • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome[6] • Immunomodulatory effects	**New York Department of Health Study on HCQ With or Without AZM:** • A retrospective, multicenter, observational study in New York evaluated the use of HCQ with and without AZM in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into 4 treatment groups: HCQ plus AZM, HCQ alone, AZM alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an ECG. *Results:* • Patients in the 3 treatment groups had more severe disease at baseline than those who received neither drug. • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug. • Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05). *Limitations:* • Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. *Interpretation:* • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest. **Observational Study of HCQ at a Large Medical Center in New York City:[10]** • This observational study evaluated 1,376 consecutive adults with COVID-19 who were admitted to a large New York City hospital (after excluding 70 patients who died or who were transferred within 24 hours after presenting to the emergency department). The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received HCQ at baseline or during follow-up.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			Patients who received HCQ were prescribed a twice-daily dose of HCQ 600 mg on the first day and 400 mg daily for 4 additional days; this was based on the clinical guidance of the hospital. *Results:* • 811 patients (58.5%) received HCQ and 565 (41.1%) did not. • Patients who received HCQ were older and more likely to have hypertension (49.1% vs. 6.7%) and to be on systemic steroids (26.6% vs. 10.1%) than those who did not receive HCQ. • Patients who received HCQ were more likely to receive concomitant AZM (59.9% vs. 22.5%) and/or other antibiotics (74.5% vs. 54.0%) than those who did not receive HCQ. • Patients who received HCQ had higher levels of inflammatory markers. • HCQ-treated patients had more severe hypoxia, with a lower PaO_2/FiO_2 ratio at baseline than patients who did not receive HCQ (median of 233 mm Hg vs. 360 mm Hg). • Most patients (85.9%) received HCQ within 48 hours of presentation. • Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). • There was also no association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31). *Limitations:* • Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. *Interpretation:* • The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study. **Retrospective Observational Cohort from the United States Veterans Health Administration** *This study has not been peer reviewed*[11] • An observational, retrospective cohort study analyzed data from patients with confirmed COVID-19 who were hospitalized at the United States

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			Veterans Health Administration medical centers between March 9–April 11, 2020. Patients were categorized as having received either HCQ, HCQ plus AZM, or no HCQ. Doses and duration of HCQ or AZM use were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic data, comorbidity data, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if BMI, vital signs, and discharge disposition were noted in their medical records. *Results:* • 368 patients were eligible for analysis. These patients were categorized into 3 treatment groups: HCQ (n = 97), HCQ plus AZM (n = 113), or no HCQ (n = 158). The median ages for the patients in each group were 70, 68, and 69 years, respectively. All patients were male. • 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation. • No difference was observed between the groups in the risk of mechanical ventilation. • The risk of death from any cause was higher in the HCQ group than in the no HCQ group (adjusted HR 2.61; 95% CI, 1.10–6.17; $P = 0.03$). The no HCQ group and the HCQ plus AZM group had similar risks of death from any cause (adjusted HR 1.14; 95% CI, 0.56–2.32, $P = 0.72$). • There was no between-group difference in the risk of death after ventilation. *Limitations:* • The patient population was entirely male. • The dose and duration of administration for HCQ and AZM were not included in the report. Patients were included if they received a single dose of either or both drugs. • Propensity score adjustment was used to account for differences between the groups; however, the possibility of residual confounding cannot be excluded, as patients who were more ill may have been more likely to receive HCQ. • No imaging data were presented; the severity of chest X-ray findings could predict worse outcomes.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			• The use of other antiviral or immunomodulatory agents were not reported. • The reason for the high mortality rate among patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild or moderate disease at admission. *Interpretation:* • This study showed no beneficial effect of HCQ plus AZM for the treatment of COVID-19 and a possible association between the use of HCQ and an increased risk of mortality; however, residual confounding may have affected the study results. **Randomized, Controlled Trial of HCQ vs. SOC for Mild or Moderate COVID-19:**[12] • This multicenter, randomized, open-label trial compared HCQ 1,200 mg once daily for 3 days followed by HCQ 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild or moderate COVID-19 [99% of the patients] and 3 weeks for 2 patients with severe disease) and SOC. • The primary outcome was a negative PCR test result within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO_2 >94% on room air, resolution of respiratory symptoms), improvement in markers of inflammation (including CRP levels), and improvement of lung lesions on a chest X-ray within 28 days. *Results:* • 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset. • The HCQ arm and the SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants, respectively) and similar times to negative PCR conversion (median of 8 days vs. 7 days, respectively). • There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis. • AEs occurred in 30% of the participants in the HCQ arm (most commonly diarrhea) and in 9% of the participants in the SOC arm. *Limitations:* • It is unclear how the overall rate of symptom alleviation was calculated.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			• The duration of HCQ use (2 weeks) was longer than in most other observational cohort studies or clinical trials for the treatment of COVID-19. • The study did not reach the target sample size. *Interpretation:* • This study demonstrated no difference in viral clearance between HCQ and SOC. **Observational Cohort of HCQ vs. No HCQ:**[13] • This observational, retrospective cohort study analyzed data for adult patients who were hospitalized for COVID-19 pneumonia at 4 French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18–80 years were eligible if they had PCR-confirmed SARS-CoV-2 infection and required oxygen by mask or nasal cannula. Exclusion criteria included HCQ initiation before hospitalization, receipt of another experimental COVID-19 treatment within 48 hours, organ failure that required immediate admission to the ICU or continuous care unit, admission with ARDS that required noninvasive ventilation with continuous positive airway pressure or mechanical ventilation, discharge from the ICU to standard care, or if a decision was made to limit or stop active treatments prescribed at admission. Patients in 1 treatment arm received a daily dose of HCQ 600 mg within 48 hours of admission; patients in the other arm did not receive HCQ during the same period. The decision to use HCQ to treat a patient was based on local medical consensus and prescriber opinion and was reportedly independent of patient characteristics. Patients were followed from baseline until death, loss to follow-up, or the end of the follow-up period on April 24, 2020. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization. *Results:* • Of the 181 patients who were eligible for the analysis, 84 participants received HCQ within 48 hours, 8 received HCQ beyond 48 hours, and 89 did not receive HCQ. • Comorbidities were less common in the HCQ group; overall initial COVID-19 severity was well balanced across the treatment arms. • In the HCQ group, 18% of the patients received concomitant AZM and 52% of the patients received amoxicillin/clavulanic acid. • In the inverse probability of treatment weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ group (76% of participants) and the non-HCQ group (75% of participants). Similarly, there was

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			no difference between the groups in the secondary outcomes of survival rate and survival rate without ARDS at Day 21. • Among the 84 patients who received HCQ within 48 hours, 8 patients (10%) experienced ECG changes that required treatment discontinuation at a median of 4 days from the start of dosing, including 7 patients with a QTc that prolonged >60 ms and 1 patient with new onset, first-degree AV block. None of these patients received AZM. *Limitations:* • This was a retrospective, nonrandomized study. *Interpretation:* • In this retrospective study, there was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not. **A Case Series of HCQ vs. Control:**[14] • In a case series from France, 26 hospitalized adults with either asymptomatic SARS-CoV-2 infection or upper or lower respiratory tract infection received HCQ 200 mg 3 times daily for 10 days. These patients were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic). *Results:* • 6 patients in the HCQ group were excluded from the analysis for the following reasons: • 1 patient died, • 3 patients were transferred to the ICU, • 1 patient stopped the study drug due to nausea, *and* • 1 patient withdrew from the study. • 6 patients also received AZM. • By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and 2 of 16 controls (12.5%). • Among the HCQ patients, 8 of 14 (57.1%) who received only HCQ and 6 of 6 (100%) who received HCQ and AZM had negative NP PCRs by Day 6. • Clinical outcomes were not reported for all patients.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			*Limitations:* • The sample size of the series is small. • The criteria for enrollment of cases and controls is unclear. • Asymptomatic individuals were enrolled. • Exclusion of 6 HCQ-treated patients includes 1 death and 3 ICU transfers. • No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown. • The reason for the addition of AZM for some patients is unclear. *Interpretation:* • Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of HCQ with or without AZM.
Hydroxychloroquine Plus Azithromycin	See the Azithromycin and Hydroxychloroquine sections above.	See the Azithromycin and Hydroxychloroquine sections above.	**Case Series of HCQ Plus AZM:**[15] • In a case series of 80 hospitalized patients with COVID-19 (including 6 patients from a previous study),[14] patients were treated with HCQ 200 mg 3 times daily for 10 days plus AZM 500 mg once daily for 1 day followed by AZM 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. The outcomes that were evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, SARS-CoV-2 level as determined by PCR, SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward. *Clinical Results:* • 1 patient died (1.2%), 3 required ICU transfer (3.8%), and 12 required oxygen therapy (15%). • 65 patients (81.2%) were discharged to their homes or transferred to other units for continuing treatment; 14 patients (17.4%) remained hospitalized at the time the study results were published. *Laboratory Results:* • SARS-CoV-2 NP PCR was negative in 83% of patients by Day 7 and in 93% of patients by Day 8. • In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine Plus Azithromycin, continued			*Limitations:* • The trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment. • The trial lacked complete or longer-term follow-up. *Interpretation:* • The multiple issues with trial design and the lack of a control group limit the usefulness of this study for informing recommendations. **Small Prospective Case Series of HCQ Plus AZM:**[16] • A prospective case series from France assessed 11 consecutive hospitalized patients with COVID-19. *Results:* • 8 of the 11 patients had significant comorbid conditions: obesity (n = 2), solid cancer (n = 3), hematological cancer (n = 2), and HIV infection (n = 1). • 10 of 11 patients were receiving supplemental oxygen at treatment initiation. • All patients were treated with HCQ 600 mg once daily for 10 days and AZM 500 mg once daily for 1 day followed by AZM 250 mg once daily for 4 days. • Within 5 days, the condition of 3 patients worsened, including 1 patient who died and 2 patients who were transferred to the ICU. • HCQ was discontinued in 1 patient due to QTc prolongation. • Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in 8 of 10 patients. *Limitations:* • This is a case series that included a small number of patients. *Interpretation:* • In this small case series, most patients who received HCQ plus AZM did not have rapid viral clearance. **Case Series of Changes in QTc Interval in Patients Who Received HCQ Plus AZM:**[17] • A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days) and AZM (500 mg once daily for 5 days).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine Plus Azithromycin, continued			*Results:* • 84 patients were enrolled; 74% were male, with a mean age of 63 ± 15 years. 65% had HTN, mean serum creatinine was 1.4 mg/dL at baseline, 13% required vasopressors, and 11% had CAD. • Some participants were receiving concomitant drugs that had the potential to prolong the QTc interval; 11% of participants were receiving neuropsychiatric drugs and 8% of participants were receiving levofloxacin, LPV/r, or tacrolimus. • 4 patients died, without arrhythmia. • The mean baseline QTc was 435 ± 24 ms and the mean maximum QTc was 463 ± 32 ms. • The mean time to maximum QTc was 3.6 ± 1.6 days. ECG follow-up was done for a mean of 4.3 days. • 9 patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively. *Limitations:* • This was a descriptive case series. *Interpretation:* • This case series demonstrated that HCQ plus AZM can prolong QTc and that the use of this combination warrants careful monitoring.
HIV Protease Inhibitors **Note:** LPV/r and DRV/c have been studied in patients with COVID-19.	HIV infection	• No data on *in vitro* activity of LPV/r against SARS-CoV-2 • Possible inhibition of SARS-CoV-2 protease 3CLpro[18] • *In vitro* data does not support the use of DRV/c for the treatment of COVID-19[19]	**LPV/r Pharmacokinetics in Patients With COVID-19:** • In a case series, 8 patients with COVID-19 were treated with LPV/r 400 mg/100 mg orally twice daily and had plasma trough levels of LPV drawn and assayed by liquid chromatography-tandem mass spectrometry.[20] *Results:* • The median plasma LPV concentration was 13.6 µg/mL. • After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the *in vitro* EC_{50} for SARS-CoV-2. *Limitations:* • Only the trough levels of LPV were quantified. • No data are available on effective LPV concentrations for SARS-CoV-2 *in vivo*.

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HIV Protease Inhibitors, continued			*Interpretation:* • The plasma drug concentrations that were achieved using typical doses of LPV/r are far below the levels that may be needed to inhibit SARS-CoV-2. **Randomized Controlled Trial of LPV/r vs. SOC:** • In a clinical trial that randomized 199 patients to receive LPV/r 400 mg/100 mg PO twice daily for 14 days or SOC, patients who were randomized to the LPV/r arm did not have a shorter time to clinical improvement. *Results:* • There was a lower, but not statistically significant, mortality rate for the LPV/r group (19.2%) than for the SOC group (25.0%), and a shorter ICU stay for those in the LPV/r group than those in the SOC group (6 days vs. 11 days; difference of -5 days; 95% CI, -9 to 0 days). • The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the LPV/r and SOC arms. • Nausea, vomiting, and diarrhea were all more frequent in the LPV/r-treated group. • The study was powered only to show a fairly large effect. *Limitations:* • The study was not blinded, which may have affected the assessments of clinical improvement. • The study was underpowered to show small effects. *Interpretation:* • A moderate-sized, randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC. **LPV/r Plus IFN Beta-1b Plus Ribavirin for COVID-19:** • Also see Interferons for a description of this trial and its results.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
HIV Protease Inhibitors, continued			• An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included IFN beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus LPV/r 400 mg/100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of LPV/r 400 mg/100 mg every 12 hours alone.[21] • In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, IFN beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only 1 participant was mechanically ventilated. *Results:* • Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group. *Limitations:* • Participants in both arms received LPV/r, so it is impossible to determine whether LPV/r contributed to the observed treatment effects. However, the possibility that LPV/r may have contributed to the effectiveness of the combination therapy also cannot be ruled out. • The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset. • Most participants in this study had mild illness, and only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States. *Interpretation:* • This study neither supports nor refutes the use of LPV/r with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
HIV Protease Inhibitors, continued			**LPV/r vs. Umifenovir vs. SOC** • In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to receive LPV/r, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received SOC.[22] *Results (Comparison of LPV/r to SOC):* • The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving LPV/r (mean 9 days [SD ± 5.0]) and for those receiving SOC (mean 9.3 days [SD ± 5.2]). • Progression to severe illness occurred among 6 patients (18%) in the LPV/r arm and 2 patients (12%) who received SOC. • 2 patients became critically ill; both were randomized to receive LPV/r. *Limitations:* • The trial had a small sample size. • The study was not blinded. • The effectiveness of umifenovir in treating COVID-19 is unknown. *Interpretation:* • The small sample size of this trial limits its usefulness. **LPV/r vs. CQ:** • A small randomized study in China compared LPV/r to CQ. Please refer to the Chloroquine section above for the study description.
Remdesivir (GS-5734)	• Not approved by FDA	• Binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription • Has demonstrated *in vitro* activity against SARS-CoV-2[4] • In a rhesus macaque model of SARS-CoV-2 infection, RDV treatment was initiated soon after inoculation; RDV-treated animals had lower lung virus levels and less lung damage than the control animals.[23]	**Multinational Randomized Controlled Trial of RDV vs. Placebo in Hospitalized Patients:[24]** • ACTT is an NIH-sponsored, multinational, randomized, double-blind placebo-controlled trial in hospitalized adults with COVID-19. Participants were randomized 1:1 to receive IV RDV or placebo for 10 days. The primary study endpoint was time to clinical recovery, which was defined as either discharge from the hospital or hospitalization for infection control purposes only. Severity of illness at baseline and at Day 15 was assessed using an ordinal scale: 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov

Remdesivir, continued			3. Hospitalized, no active medical problems
			4. Hospitalized, not on oxygen
			5. Hospitalized, on oxygen
			6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation
			7. Hospitalized, on mechanical ventilation or ECMO
			8. Death
			Study Population:
			• The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection. Patients were enrolled if they met at least 1 of the following conditions:
			  • The patient had pulmonary infiltrates, as determined by radiographic imaging,
			  • SpO_2 was ≤94% on room air,
			  • The patient required supplemental oxygen,
			  • The patient was on mechanical ventilation, *or*
			  • The patient was on ECMO.
			• The study excluded individuals who had ALT or AST levels >5 times the ULN, those who had an eGFR <30 mL/min, and those who were pregnant or breastfeeding.
			Preliminary Results:
			• Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the RDV group; n = 521 for the placebo group).
			• The mean age was 58.9 years; 64.3% of participants were male, 53.2% were white, and 79.8% were enrolled in North America.
			• 52.1% of participants had 2 or more comorbidities; 37% were obese (mean BMI 30.6 kg/m^2)
			• The median time from symptom onset to randomization was 9 days (IQR 6–12 days).
			• At the time of the preliminary analysis, 391 RDV recipients and 340 placebo recipients had completed the study through Day 29, recovered, or died.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			• 8 RDV recipients and 9 placebo recipients terminated the study prior to Day 29. • At the time of this preliminary analysis, 132 RDV recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit. • RDV significantly reduced time to recovery compared to placebo (median time to recovery 11 days vs. 15 days, respectively; recovery rate ratio 1.32; 95% CI, 1.12–1.55; $P < 0.001$). • Clinical improvement based on the ordinal scale was significantly higher in patients who received RDV than in those who received placebo at Day 15 (OR 1.50; 95% CI, 1.18–1.91, $P < 0.001$). • The benefit of RDV on reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 421; recovery rate ratio 1.47; 95% CI, 1.17–1.84). In a post-hoc analysis of 14-day survival, remdesivir appeared to confer a survival benefit in this subgroup (HR 0.22; 95% CI, 0.08–0.58). • In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 197), there was no observed difference between the remdesivir and placebo groups in time to recovery (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In a post-hoc analysis of 14-day survival, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38). • Among the patients who were on mechanical ventilation or ECMO at enrollment (ordinal scale 7, n = 272), there was no observed difference between the RDV and placebo groups in time to recovery (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In a post-hoc analysis of 14-day survival, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92). • Among the patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the RDV and placebo groups (n = 119; recovery rate ratio 1.09; 95% CI, 0.73–1.62). Mild to moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/min without supplemental oxygen. • The mortality estimate by Day 14 was lower in the RDV arm than in the placebo arm (7.1% vs. 11.9%, respectively), but the difference was not statistically significant (HR 0.70; 95% CI, 0.47–1.04).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			• The use of RDV was associated with shorter time to recovery regardless of the duration of symptoms prior to randomization (≤10 days vs. >10 days). • The percentages of participants with serious AEs were similar in the RDV and placebo groups (21.1% vs. 27.0%, respectively). • Transaminase elevations occurred in 4.1% of RDV recipients and 5.9% of placebo recipients. *Limitations:* • At the time of publication, the full dataset was not available for analysis. *Interpretation:* • In patients with severe COVID-19, RDV reduced the time to clinical recovery. The benefit of RDV was most apparent in hospitalized patients who required only supplemental oxygen. There was no observed benefit of RDV in those who were on high-flow oxygen, noninvasive ventilation, mechanically ventilation or ECMO, but the study was not powered to detect differences in subgroups. There was no observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small. **Multinational Randomized Trial of Different Durations of RDV Treatment in Hospitalized Patients:**[25] • This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV RDV. The primary study endpoint was clinical status at Day 14, which was assessed using a 7-point ordinal scale: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices 4. Hospitalized, requiring low-flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons 6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for RDV administration) 7. Not hospitalized

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			*Study Population:* • The study enrolled hospitalized patients aged ≥12 years with RT-PCR-confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates. Patients in this study had either SpO_2 ≤94% on room air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated CrCl <50 mL/min. Patients were also excluded if they had received an agent with putative anti-SARS-CoV-2 activity within 24 hours of starting treatment in the trial. *Results:* • Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of RDV treatment. • In the 5-day group, the median age was 61 years; 60% of participants were male, and 71% were white. In the 10-day group, the median age was 62 years; 68% of participants were male, and 70% were white. The frequency of coexisting conditions was similar in both groups. • The median time from symptom onset to first dose of RDV was 8 days in the 5-day group and 9 days in the 10-day group. The median duration of hospitalization before the first RDV dose was 2 days in both groups. • At baseline, patients in the 10-day group had worse clinical status (based on the ordinal scale distribution) than those in the 5-day group (P = 0.02). • A few patients were on mechanical ventilation: 4 patients (2%) were assigned to the 5-day group, and 9 patients (5%) were assigned to the 10-day group. Although mechanical ventilation was an exclusion criterion for enrollment, some patients were intubated between screening and treatment initiation; others were protocol deviations. • 172 participants (86%) in the 5-day group completed a median of 5 days of treatment, and 86 (44%) in the 10-day group completed a median 9 days of treatment. • 65% of patients in the 5-day group and 54% of those in the 10-day group had a 2-point improvement in clinical status on the ordinal scale. • After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups (P = 0.14)

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			• The time to clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days, respectively). • The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10 days) and 10-day group (8 days; IQR 5–10 days). • By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 patients (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 patients (11%) had died. • Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%); 4% of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs. *Limitations:* • This was an open-label trial without a placebo control group, so the clinical benefit of RDV could not be assessed. • There were baseline imbalances in the clinical statuses of participants in the 5-day and 10-day groups. At the start of the study, more patients in the 10-day group than in the 5-day group were receiving noninvasive ventilation or high-flow oxygen (30% vs. 24%, respectively), and fewer patients in the 10-day group than in the 5-day group were not receiving supplemental oxygen (11% vs. 17%, respectively). *Interpretation:* • In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had similar clinical benefit. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of RDV treatment for critically ill patients is still unclear. **Randomized Controlled Trial of RDV vs. Placebo for Severe COVID-19 in China:**[26] • This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China. Patients were randomized 2:1 to receive IV RDV or normal saline placebo for 10 days. Concomitant use of LPV/r, corticosteroids, and interferons was allowed.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients. • The study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days, whose O_2 saturation was ≤94% on room air or whose PaO_2/FiO_2 was <300 mmHg, and who had radiographically confirmed pneumonia. *Results:* • Between February 6–March 12, 2020, 237 hospitalized patients were enrolled and randomized to receive RDV (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China. • The participants' median age was 65 years; 56% of the participants in the RDV arm and 65% in the placebo arm were male. • There were more patients with HTN, DM, or CAD in the RDV arm than in the placebo arm. • At Day 1, 83% of the patients required supplemental oxygen by nasal cannula or mask; only 1 patient required mechanical ventilation or ECMO. • The median time from symptom onset to randomization was 9 days in the RDV group and 10 days in the placebo group. • 65% of participants in the RDV group and 68% of participants in the placebo group received corticosteroids. • 28% of participants in the RDV group and 29% of participants in the placebo group received LPV/r. • 29% of participants in the RDV arm and 38% of participants in the placebo arm received IFN alfa-2b. *Study Endpoints:* • There was no difference in the time to clinical improvement between the RDV and placebo groups (a median of 21 days vs. 23 days, respectively; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen in the RDV arm than in the placebo arm (median of 18 days vs. 23 days, respectively; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			• The 28-day mortality rate was similar for the 2 study arms (14% of participants in the RDV arm vs. 13% in the placebo arm). • There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the 2 groups. • The number of participants who experienced AEs was similar between the 2 groups (66% of participants in the RDV arm vs. 64% in the placebo arm). • More participants in the RDV arm discontinued therapy due to AEs (12% of participants in the RDV arm vs. 5% in the placebo arm). *Limitations:* • The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes. • The use of concomitant medications (i.e., corticosteroids, LPV/r, IFNs) may have obscured the effects of RDV. *Interpretation:* • There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between RDV-treated and placebo-treated patients. **Uncontrolled Case Series from RDV Compassionate Use Program** • In an uncontrolled case series of 53 hospitalized patients with COVID-19, most patients needed less oxygen support after receiving compassionate use RDV. There was no comparison group, however, so it is not possible to assess whether the improvement was the result of using RDV.[27]

Key: 3CLpro = 3-chymotrypsin-like protease; ACE2 = angiotensin-converting enzyme 2; ACTT = Adaptive COVID-19 Treatment Trial; AE = adverse effect or adverse event; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CQ = chloroquine; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; DM = diabetes mellitus; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; EC_{50} = half-maximal effective concentration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; IFN = interferon; IL = interleukin; IQR = interquartile range; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NIH = National Institutes of Health; NP = nasopharyngeal; OR = odds ratio; PCR = polymerase chain reaction; PO = orally; QTcF = corrected QT interval by Fredericia; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; STI = sexually transmitted infection; ULN = upper limit of normal

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Table 2b. Characteristics of Potential Antiviral Agents Under Evaluation for Treatment of COVID-19

Last Updated: July 17, 2020

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data from patients with COVID-19, when available.
- The effective dosing of these drugs for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs in patients with COVID-19 are not well defined; the validity of extrapolation between patient populations (i.e., FDA-approved use vs. COVID-19 use) is unknown, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table, because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labeling, and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin **Note:** Most studies of COVID-19 use AZM with HCQ.	AZM 500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5	• Gastrointestinal effects (e.g., diarrhea, nausea, vomiting) • Hepatotoxicity	• Baseline ECG and follow-up ECG • Hepatic panel, SCr, potassium, magnesium	Additive effect with other drugs that prolong the QTc interval (including HCQ and CQ)	• The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Half-life of up to 72 hours • A list of clinical trials is available here: Azithromycin

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine	**Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg:** • CQ 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash • Given the risk of heart rhythm problems, the FDA cautions against using CQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if CQ is given with QTc-prolonging drugs or if the patient has underlying cardiac disease • Perform G6PD testing; CQ **is not recommended** in patients with G6PD deficiency. Consider using HCQ instead of CQ while awaiting G6PD test results.	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of CQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. • Dose-dependent toxicity • CQ is not commercially available in the United States. • A list of clinical trials is available here: Chloroquine
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:** • HCQ 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if HCQ is given with QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac disease	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of HCQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Hydroxychloroquine, continued		• Allergic reaction/rash • Given the risk of heart rhythm problems, the FDA cautions against the use of HCQ to treat COVID-19 outside of a hospital or a clinical trial.[1]			• A list of clinical trials is available here: Hydroxychloroquine
Lopinavir/Ritonavir	**Adults:** • LPV/r 400 mg/100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • LPV 300 mg/m2 plus RTV 75 mg/m^2 (maximum: LPV/r 400 mg/100 mg per dose) PO twice daily for a total of 7 days	• Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Transaminase elevation • QTc interval prolongation and Torsades de Pointes have been reported. • PR interval prolongation	• HIV antigen/antibody testing at baseline • Serum transaminase levels • Consider monitoring ECG when LPV/r is given with other QTc-prolonging medications.	**High Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > CYP2D6 substrate • Potent CYP3A4 and CYP2D6 inhibitor • Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19	• The Panel **recommends against** the use of LPV/r and other HIV PIs for the treatment of COVID-19, except in a clinical trial **(AI)**. • Liquid formulation is commercially available. Crushing LPV/r tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[2] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir **Note:** RDV is not approved by the FDA; however, it is available through an EUA,[a] a clinical trial, or the manufacturer's emergency access program.	**In Patients Who Are Participating in Clinical Trials:** • Dose according to the clinical trial protocol. **Panel's Recommendations for Adult and Pediatric Patients Weighing ≥40 kg** *For Patients With Severe COVID-19 Who Are Not Intubated:* • RDV 200 mg IV over 30–120 minutes for 1 dose, followed by RDV 100 mg IV on Day 2 through Day 5 **(AI)**. *For Mechanically Ventilated Patients, Patients on ECMO, and Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:* • There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, and patients who have not shown adequate improvement after 5 days of therapy. Some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **Note:** The EUA recommends 10-day therapy for patients on mechanical ventilation or ECMO. **Suggested Dose in EUA[a] for Pediatric Patients Weighing 3.5 to <40 kg** *For Patients Who Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 10	• Transient elevations in ALT or AST levels (Grade 1 or 2), typically after multiple days of therapy[3] • Mild, reversible PT prolongation without INR change or hepatic effects[3] • Drug vehicle is SBECD, which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Gastrointestinal symptoms (e.g., nausea, vomiting)	• Monitor for infusion reactions. • Renal and hepatic function • **Do not administer** RDV if eGFR is <30 mL/min (or if patient is receiving dialysis), or if ALT or AST level is >5 times ULN	• Clinical studies of drug-drug interactions for RDV have not been conducted. • RDV levels are unlikely to be substantially altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters. • RDV may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. • Strong induction may modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. Based on information provided by Gilead (written communication, July 2020), the use of RDV with strong inducers (e.g., rifampin) **is not**	**Recommendation for Prioritizing Limited Supplies of Remdesivir:** • Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO **(BI)**. **Recommendation for Patients with Mild or Moderate COVID-19:** • There are insufficient data for the Panel to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19. **Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO:** • The Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first **(AI)**. • If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen,

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued	*For Patients Who Do Not Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 5. If there is no clinical improvement, treatment may be extended for up to 5 additional days (for a total treatment duration of 10 days).			**recommended**. • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone. • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.	noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed. **Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO:** • Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir. **Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy:** • There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**. **Availability:** • RDV is available through an EUA[a] for the treatment of hospitalized adults and children with severe COVID-19. • RDV is also available for other patient populations through expanded access and compassionate use programs. • A list of clinical trials is available here: Remdesivir

[a] The FDA EUA permits the emergency use of the investigational product RDV for the treatment of suspected COVID-19 or laboratory-confirmed COVID-19 in adults and children who have been hospitalized with severe disease. Severe disease is defined as COVID-19 in patients with SpO_2 ≤94% on room air (at sea level) or in patients who require supplemental oxygen, mechanical ventilation, or ECMO.

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; AV = atrioventricular; AZM = azithromycin; CBC = complete blood count; CQ = chloroquine; CYP = cytochrome P; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PI = protease inhibitor; PMA = postmenstrual age; PO = orally; PT = prothrombin time; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether-beta-cyclodextrin sodium; SCr = serum creatinine; UGT = uridine diphosphate glucuronosyltransferase; ULN = upper limit of normal

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